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Tetanus

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TETANUS

by

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Contents

Introduction

"An inhuman calamity! An unseemly sight! A spectacle painful even to the beholder! An incurable malady! Owing to the distortion, not to be recognized by the dearest friends; and hence the prayer of the spectators, which formerly would have been reckoned not pious, now becomes good, that the patient may depart from life as being a deliverance from the pains and unseemly evils attendant on it". Thus has the ancient Aretaeus pictured the sufferings of tetanus (7). The picture remains the same today.

During the past year I had the opportunity of treating various wounds, mostly of a trivial nature, but some of a more serious type. In my opinion, a certain number of these required a prophylactic injection of tetanus antitoxin. In this way my interest in the problem of tetanus in general was aroused. I soon found after a small amount of reading that the treatment of tetanus is in a decidely confused state and also that the pathogenesis of tetanus presents a variance in theories. Treatment of any disease can hardly be expected to be successful if based on an erroneous pathogenesis.

This thesis gives me the opportunity to present

arguments favoring the modern thought concerning the pathogenesis of tetanus, along with definite improvements in the treatment of the disease.

I have not attempted anything even approaching a complete resume of the literature on the treatment of tetanus. Such a work would be monumental, confusing, contradictory and of little use to the man attempting to treat a single case of tetanus.

TETANUS

Definition

Tetanus is an acute infectious disease characterized by painful tonic spasms of the muscles, and caused by a soluble toxin elaborated by the Clostridium tetani. The muscles of mastication, the masseters and pterygoids are most commonly involved.

History

Tetanus was known and described by Hippocrates as well as Aretaeus (second century A.D.). Since those early periods of Medicine it has been described frequently. Theories as to its etiology were many and strange, but it was not until the latter part of the 19th century that tetanus was proven to be caused by a micro-organism.

Kitosato (1889) is credited with first having obtained pure cultures of the tetanus bacillus. With his pure cultures he produced typical tetanus in animals. After death, the lesions he found were trivial and the bacillus had a very limited distribution. He could not recover the organism from the body after death and suggested that it disappeared quickly after

producing some very active chemical poison.

In 1890 Behring and Kitosato published their classical paper on immunization against tetanus. They showed that the cell-free blood serum of animals inoculated with tetanus toxin neutralized the toxin and rendered it inert. This antitoxic action became the basis of the serotherapy of tetanus, which was soon made available for practice. In succeeding years it became evident that the antitoxic treatment of tetanus was not all that had been hoped for. The use of antitoxin in tetanus treatment caused the hope to sweep through the world that the problem was solved. But then it was discovered that the toxin-nerve cell union was not disrupted by antitoxin. That the failure of antitoxin to cure tetanus was due to the localization of the toxin in the central nervous system was disclosed particularly through the work of Ransom (1900) and Meyer and Ransom (1903), (14). This led to a wave of serum nihilism sweeping through the literature and scores of various sedative treatments came into great popularity. In the past 15 years dependence on serum has somewhat revived with the reports of low mortality rates after use of large doses of tetanus antitoxin (20).

Incidence

There are about 1500 deaths from tetanus in the United States each year. A survey of a recent yearly mortality report from the U. S. Census Bureau shows about one death from tetanus in 1071 deaths for the whole country. The highest rate is in cities of 2500 to 10,000 population, and the lowest is in the rural areas. The southern states show the highest incidence while the coastal states have the lowest rate. The midwestern states average about that of the nation as a whole. In civil life tetanus is most frequent in children. The usual incidence in sex is 75% in males and 25% in females. This is easily and accurately accounted for by the rough and tumble manner of recreation of the male child, and the higher incidence of wounds in general of adult males due to occupational pursuits.

In the southern states of the United States, particularly those bordering the Gulf of Mexico, the incidence of tetanus is higher than for the other states according to Moore and Singleton (44). They believe there are many factors responsible for this. The climate is moist and warm; there is no freezing the year around; a great percentage of the people are engaged in agricultural occupations, and the protection

afforded by shoes is a luxury to most of them. Poor social conditions and grossly inadequate medical care help to contribute to this greater incidence in the south.

Before the use of antitetanus serum prophylactically the incidence always increased during war. In World War I all of the American troops who were wounded were injected with antitoxin. Of 224,089 wounded only 36 developed tetanus. This is an incidence of 0.016%, the lowest ever recorded during warfare.(17)

In Nebraska, based on the years 1933, '34 and '35, there are 5 to 10 deaths per million people per year. The incidence of tetanus cases in this hospital (University) in the period 1932-1940 inclusive was 11 cases in 35,618 admissions, or .0003%. (55).

Kini and Rao of India (34) discuss 38 cases of tetanus in 4,416 hospital admissions or an incidence of 0.86%. This substantiates the claim that the incidence is higher in warm, moist climates.

Etiology

The etiological agent of tetanus, the Clostridium tetani, is a gram-positive spore-forming bacillus which is strictly anaerobic. Its natural habitat is

the intestinal tract of man and animals. The organism is frequently found in the feces of horses, cattle and sheep, but to a considerably less extent in the intestinal tract of man. A study of fecal discharges of urban dwellers reveals an incidence of less than 5% (14).

When tetanus occurs there is practically always a history of an injury which has caused a break in the continuity of the skin surface. Certainly it occurs after trifling wounds, but in most cases it follows extensive injury. Tetanus organisms in pure culture are practically harmless when injected into the normal tissues of susceptible animals, but if the tissues are injured by mechanical or chemical means or by concurrent infection with other bacteria, the tetanus bacilli multiply and produce toxin (41).

The most important predisposing cause of tetanus is the wound. It may range from the minute puncture of a hypodermic needle to a shell laceration. It occurs in soil contaminated wounds, infected abortions, insect bites, infected umbilical stumps (tetanus neonatorum), blank cartridge burns, compound fractures, bedsores, blisters on the feet, and puncture wounds from contaminated splinters and nails (12). It is

particularly prone to follow powder burns.

It is probably not generally appreciated that the wool wadding in blank cartridges is nearly always contaminated with tetanus spores or bacilli, as is most woolen clothing through which so many injuries are sustained. In treating wounds one is apt to associate with tetanus only those which are received in the garden or stable. There is no doubt that many clean foreign bodies carry with them tetanus spores from woolen clothing which they penetrate to inflict an injury. Wounds received in such a manner deserve a debridement at the very least(29).

In many cases of tetanus the atrium of infection remains completely undisclosed. This is particularly so if the primary lesion is hidden in the viscera, and thus we have the misnomer "idiopathic" tetanus. Most tetanus in children arises from wounds which are of such a trivial nature that the physician and often the mother are not consulted by the child (20).

Of the eleven cases treated at the University hospital in the period 1932-1940 the following types of wounds were responsible for the development of tetanus:

Lacerations....3

Scalp...1
Hand....1
Toe.....1

Puncture wounds....7
Foot.....3
Hand.....2
Thigh.....1
Buttock...1

Unknown Primary lesion...1

It would not be of any pertinent value at this point to give a detailed discussion of the bacteriology of the Clostridium tetani. But certain salient features in regard to its habitat and growth characteristics are important because of the intimate relationship between the type of wound and the development of clinical tetanus.

Clostridium tetanus is an anaerobe; that is, to grow and produce toxin it must have an oxygen free environment. It is because of this property that tetanus occurs most commonly in puncture wounds and lacerations. In the case of the puncture wound the bacilli or their spores are driven deeply into the tissues, and the tract of entrance is closed off from the oxygen abundant atmosphere by the sealing of the superficial portal of entry with fibrin, and thus an ideal site for the growth of the bacilli is formed.

Tetanus develops in the lacerated wound because

even though the wound is in contact with the atmospheric oxygen, the oxygen tension of the traumatized tissue is definitely lowered by the ischemia due to blood loss and by the anoxemia of the devitalized tissue. So here again we have the ideal habitat for the Clostridium tetani to grow in. The tetanus bacillus may be present in a wound without tetanus developing, if the anaerobic conditions are not present. (33)

Prophylaxis

The experience gained in the first World War has given full proof that prophylaxis against tetanus is a complete success. The figures which I have quoted above give ample evidence of the fact. British War statistics show that before the routine use of antitoxin the incidence of tetanus among the wounded was 15 to 32 per 1,000 wounded, while after its routine use the incidence never rose above 2 or 3 per 1,000 (52). The principles of good prophylaxis against tetanus are three:

1. Administer 1500 units of antitoxin subcutaneously as soon as possible after the injury.

2. Debride all necrotic and damaged tissue.

3. Never suture a contaminated wound.

The antiserum must be administered as soon as possible after injury, not merely within twelve hours. Antitoxin immunizes a patient for 10-14 days only, therefore a second and perhaps a third injection are necessary in cases of non-healing wounds, in order to prevent delayed tetanus (33).

One prophylactic effort which has borne much fruit is the nationwide outlawing of firecrackers on the Fourth of July. The most recent sane July Fourths have had almost no deaths from tetanus.

Theoretically prophylaxis should be practiced immediately upon the receipt of each and every puncture wound. If every tetanus contaminated wound was debrided, cleaned, and oxygenated, nearly all patients would be spared the agonies of the disease. Every wound must be treated as a potential seat of infection. The tract of all puncture wounds should be incised, enlarged, properly cleansed, drained and covered with continuous hot compresses. Every effort must be made to remove all foreign material. Actual scrubbing of a wound with a sterile brush is not too vigorous a measure. In deep abrasive wounds a thorough debridement should be performed. Cauterization of wounds can only be condemned.

Caustics form an eschar which excludes oxygen, thereby creating a favorable medium of growth for anaerobic organisms. In addition to lowering the oxygen tension, additional insult is inflicted upon tissues already devitalized (10).

In treating a wound a good rule to follow is this: if any doubt exists, a prophylactic injection of tetanus antiserum is indicated. Patients who have received a prophylactic injection, but develop tetanus regardless, have a greatly lengthened incubation period. This is delayed tetanus, and is apt to occur if the causative wound has not received proper attention. In such cases it is common for a local abdominal form of tetanus to develop (43).

1,500 units of antitoxin can be woefully inadequate in protecting a patient who has a compound fracture. Dietrich (20) discusses three cases which were compound fractures, and all of which received 1,500 units of antitoxin; nevertheless, all three developed tetanus, and two of them died. Moore and Singleton (44) review 2 cases in their series of 102, which developed fatal tetanus after prophylactic serum injection. One, a child, developed fatal tetanus four days after receiving 4,000 units of antitoxin. The other was an adult diabetic, who developed tetanus twelve

days after suffering a compound dislocation of a toe resulting in gangrene of the foot, but only three days after receiving 3,000 units of tetanus antiserum.

In the average case of injury, 1,500 units of tetanus antitoxin generally is sufficient, regardless of the patient's age. Prior to administration, every effort should be made to obtain a careful history of previous allergic reactions, such as asthma or urticaria, and also a record of serum inoculations. These precautions should be supplemented by skin testing. When a positive history or skin test is obtained, the attending physician must make the final decision. He must weigh a potential case of tetanus because of the type of injury he is dealing with, against a possible fatal anaphylactic reaction resulting from the use of antitoxin. In place of a single dose, according to Best (10), his clinical experience has shown that acute serum reactions are less apt to occur if antitoxin is given in divided doses over a period of 45 to 60 minutes. In extensive injuries, 1,500 units can be given at once and repeated in 24 hours. However, when two doses are contemplated, it is not amiss to give only one dose of 3,000 units (42). It must again be reiterated that 1,500 units of antitoxin do not afford invariable protection.

Pathology

There are no clinical features of a wound which are pathognomonic of tetanus infection. The wound may be very harmless appearing and of only a trivial nature. Gross examination at autopsy will show no findings whatever, to characterize a tetanus death. The marked antemortem rigor of tetanus disappears at once on death.(30)

One may find some evidence of tetanus toxemia on microscopic examination of the muscles and the spinal cord, but the other tissues and organs show no changes. The muscles which were most involved will present a waxy degeneration and there will be a disappearance of the striations. In the cord there will be hemorrhage into the gray matter, and the plasm of the nerve cells becomes much more granular than usual. Also the ganglion cells become small and of a fusiform shape.(30) Other than these few changes the pathology of tetanus is meager, and this is a little difficult to conceive in view of the severity of the disease.

Pathogenesis

As I will show later, the mortality from tetanus

is very high, in my opinion much higher than it would be if the pathogenesis of the disease were thoroughly understood. It will be readily admitted, I believe, that rational treatment of tetanus, or any disease, depends on an accurate knowledge of the pathogenesis of the disease. It is my intention here to present briefly and as succinctly as possible the most recent work, and the conclusions drawn therefrom, on the pathogenesis of tetanus. Granted that many cases of tetanus are beyond help with the best of treatment, but it is heart-wrenching indeed to see or hear of a case of tetanus treated unsuccessfully because the physician has an inadequate understanding of the true manner in which the disease is progressing.

Until recently the classical theory of carriage of the toxin in the peripheral nerves, the theory of Meyer and Ransom, has been generally accepted. Their work was done in 1903 and the nerve carriage theory was published at that time. In 1917, Ransom in a paper entitled "A Modern View of Tetanus" (48) explains the pathogenesis of the disease in this manner: "Tetanus is a disease of the central nervous system and all the effects which tetanus toxin produces are due to its action upon nerve cells. The cells of the central nervous system do not pick up the toxin from

the blood stream or the lymph; the only route by which nerve cells can be attacked is via the motor nerves". And similarly his explanation for a purely local form of tetanus, i.e., involving only one limb or one group of muscles, is this: "Under the above condition the motor nerves of the infected area are at an advantage and the toxin travelling along them reaches their centres, before the rest of the toxin, which has first to be absorbed and distributed, has time to become effective. The consequence is that, other things being equal, the first symptoms of tetanus occur in the area supplied by the motor nerves about the point of infection--thus a local tetanus arises".

Further, the theory of Meyer and Ransom proposed that once the toxin reached the anterior horn cells of the spinal cord, it spread up and down within the cord to cause a descending tetanus, and also backward to involve the sensory nerve cells. The nerve-carriage theory of Meyer and Ransom has been discarded by some, but not all workers in the field of experimental tetanus. Leslie Cole, famed in Britain for his work with tetanus, vigorously supported their theory of pathogenesis in a paper published in 1937 (18).

In 1935, J. J. Abel and associates began working at Johns Hopkins University on the pathogenesis of

tetanus, and since that time they have published a large series of very convincing papers which are revolutionary in regard to the theory of Meyer and Ransom. But for the moment I will leave this, in order to discuss the disease at its inception.

Tetanus, to appear, must have the Clostridium tetani, or its spores, introduced into the tissues beneath the skin. There are innumerable ways in which this can occur. Thus it may occur during or after the application of plaster, extraction of teeth, after insect bites and stings, gunshot and knife wounds, powder burns; in fact after every kind of lesion of the body surface or its orifices. After entrance the bacillus rapidly multiplies if there is a diminished oxygen tension and if there is necrosis of tissue cells. The bacilli are not dispersed throughout the body, but multiply for a time at the site of inoculation. During the time of bacillary growth in the infected area, a highly poisonous substance--tetanus toxin, appears. This exceedingly potent, water-soluble substance has been definitely proved to be the true cause of the disease. Investigation has not established with certainty whether one or more than one tetanizing poison is produced by the bacilli, but probabilities are in favor of a single substance (1).

Now to return to the recent revolutionary work of Abel and his co-workers. They are firmly convinced and offer excellent proof that this toxin is being constantly removed from its place of origin in the wound, by the lymphatics and blood vessels, to be distributed throughout the body by the arterial current. And further they show how badly in error is the nerve carriage theory.

According to Abel (1) there were three variants of the nerve carriage theory of Meyer and Ransom. These are:

1. The toxin is actually carried in the motor nerve fibers up to the central nervous system.

2. The toxin is transported from the periphery to the central nervous system and cerebrospinal fluid by endo- and perineural lymphatic vessels of mixed nerves.

3. The toxin is carried by centripetal transport in the tissue space of the nerve trunks.

Abel has shown that all the previous investigators who supported the above three theories did not base their work on anatomical fact, but merely on conjecture; and he refutes the above three theories in this manner:

1. Protoplasmic streaming and movement of molecules in a nerve fiber is impossible. Previous experimenters who injected dye into a peripneral nerve trunk, and then noted its passage up

and down the nerve, and then concluded that this was the manner in which tetanus toxin travelled, were mistaken, because Abel proves it was merely the high pressure of the injection which forced the die to travel.

2. The lymph vessels of nerves end in lymph nodes, not in the sub-arachnoid space.

3. There are no tissue spaces, as such, in a nerve fiber.

Working with large dogs, Abel, Hampil and Jonas injected tetanus toxin directly into the sciatic nerve with the strictest aseptic technique. They injected the toxin into the center portion of the nerve trunk and after withdrawing the needle they sponged the injection site for 10 minutes in order to prevent escape of tetanus toxin from the nerve. Then the dog was immobilized for 5 days to prevent muscle action from squeezing the toxin out of the nerve. When this was done with faultless technique there were absolutely no symptoms of tetanus either localized or general that developed. As controls they injected the same amount of tetanus toxin into the muscle substance of other dogs with striking tetanizing. This absolutely shows that the tetanus toxin isn't carried by the nerve but can only be carried by the bloodstream to the central nervous system. Their deduction from this work is this: Tetanus toxin is absorbed by the haemal

and lymph capillaries at the seat of the infected wound and is carried to the various body tissues including the central nervous system only by way of the arterial blood stream (2).

The tetanus toxin must cause a profound metabolic alteration in the body, because in the course of a severe but not fatal tetanus there is marked weight loss even with undiminished caloric intake. This is seen clinically in the asthenia and emaciation of robust men during a prolonged tetanus (33). The cells of the various organs of the body including the voluntary muscles have the ability to fix the toxin that is brought to them in the circulating blood, in a chemically and biologically unrecognizable form and it is irretrievable as such from them (4). When the toxin reaches a certain concentration in the non-reactive organs whose cells are capable of absorbing it, some of them may be deranged by it in a manner consonant with their special functions, just as the voluntary muscles respond to it in their own characteristic manner (4).

The widely accepted theory is that there is a blood-brain barrier that prevents the toxin from gaining access to the neurons of the central nervous

system from the blood stream, but the experiments of Abel have proven that the motor neurons of the central nervous system, and also the motor end-plates of the voluntary muscles begin to absorb and fix in an irreversible manner their quotum of the poison from the moment it reaches them via the blood stream.

The proponents of the nerve carriage theory maintain that the toxin that has been fixed upon the neurons in the central nervous system can no longer be neutralized by tetanus antitoxin because this principle is supposedly incapable, on account of the large size of its moleculeof reaching the neurons either by way of the axis cylinders of the motor nerves or by way of the circulation. As I have already stated, the facts that were brought to light by Abel previously, have made it clear that it is only by way of the blood stream that the toxin of tetanus, as well as its antibody can reach the central nervous system. The contention of those who maintain that an impenetrable brain-blood barrier prevents circulating antitoxin molecules from reaching and neutralizing fixed toxin cannot be reconciled with the work of Abel. At the close of the experiments of Abel and his associates, they had animals in hand whose specifically reacting nervous centers

had irreversibly fixed enough of the originally injected toxin to insure death, and, note especially, all unbound toxin except a slight residue had been removed from their cardiovascular and lymphatic systems. When such animals, that had fixed a lethal amount of the toxin were injected intravenously with a large amount of antitetanic serum, they showed no symptoms of tetanus and remained entirely well; while control animals that had received no serum succumbed to tetanus induced by their fixed toxin (6). It certainly is not surprising to maintain that both tetanus toxin and its antibody can reach the motor neurons of the spinal cord and medulla by way of the blood stream, and that the so-called brain-blood barrier is freely permeable to them, when it is borne in mind that both of these principles enter and escape from the lymph and blood capillaries with the greatest ease (6).

Even though the cells in the central nervous system and in the muscles and in the other organs of the body fix the toxin in an irretrievable form, these very cells have the power to destroy or render innocuous this fixed toxin, because many cases of acute tetanus are restored to perfect health without residual damage to any organ.

Tetanus toxin exhibits both a central and a peripheral action. The central effect, which is characterized by reflex motor convulsions is due to the poisoning of the motor nerve cells of the spinal cord, medulla and pons. The peripheral effect, recognized as the unremitting rigidity of voluntary muscles, results from the fixation of the toxin upon the motor end-organs of those muscles (4).

According to Firor (23) the stiffness and rigidity that occur in local tetanus are due to the action of the toxin on the motor end-organs, while the clonic convulsions of tetanus are due to the poisoning of the anterior horn cells. After tetanus toxin reaches the anterior horn cells it becomes fixed and following this there is an incubation period before symptoms occur. It seems clear that during this period the toxin becomes altered and can no longer be neutralized by antitoxin, and this altered toxin is the common cause of death in tetanus. Although the clonic convulsions, as I have stated above are due to the involvement of the anterior horn cells in the cord, Firor and Jonas (22) present further evidence that the cause of muscular rigidity as seen in both local and general tetanus is not to be sought in an action of the toxin on special centers in the central nervous system, but in its

direct action on the voluntary muscles. In an experiment with dogs in which they deposited with a #26 guage needle, 1/4 to 1/50 of a MLD of toxin directly into the spinal cord (into the anterior horn), they found there was not the slightest evidence of muscular rigidity or tetanus dolorosus (22).

Firor and associates, in a very interesting study on the cause of death in tetanus (24), found that by injecting tetanus toxin in amounts of less than one lethal dose into the anterior horn of the lumbar cord of dogs, death resulted in 100 cases. Dogs that had less than one lethal dose injected into organs other than the central nervous system, such as veins, liver, testis and motor nerves all lived indefinitely and showed no symptoms. As further proof that toxin of the tetanus bacilli is removed from the focus of infection by the blood and lymphatic systems and distributed throughout the body to the vital centers by this means, they injected tetanus toxin into the distal end of a transected cord and found that the animals died within 10 days, of tetanus, and in the same manner as dogs having toxin injected into the intact cord. It is their belief that the respiratory center is the vital center upon which the toxin acts

to cause death. The basis for their belief is that by observing respirations they could infallibly tell when death was near. It is a common clinical observation that sudden respiratory failure is often the terminal event in patients dying of tetanus. In all the experimental animals of Firor, we noticed that in death due to tetanus the respirations ceased 3 to 5 minutes before the heart ceased beating. This suggests that drugs which are respiratory depressants should be used with extreme caution in cases of human tetanus.

Firor and Lamont in a very recent paper (21) suggest that the agent of death may not be the tetanus toxin as such, but rather a secondary product formed by the alteration of the tetanus toxin within the spinal cord. The intraspinal injection of 1/400 or more of the lethal dose of tetanus toxin always was followed by the death of the dog, despite the fact that the toxin was placed in a non-vital center, such as the lumbar cord. The explanation that death results from an upward passage of the toxin is untenable, because as I have shown above, transection of the cord above the site of injection does not prevent death. Similarly they found that division of all sensory and motor pathways below the lesion is without effect. The death

of the animal could not be caused by multiplication of the tetanus molecule and subsequent reabsorption because the presence in the circulating blood of 100 neutralizing doses of tetanus antitoxin as a previous precaution did not prevent a fatal outcome. The only explanation that can be drawn from this, at least tentatively, is that tetanus toxin is altered in the spinal cord to form a secondary substance that is responsible for death.

Knowledge as to the true pathogenesis of tetanus has certainly progressed with great strides in the past five years, but that it is not a closed and completed book is readily seen when one ponders the latest problem as proposed by Firor, discussed immediately above.

Symptoms

Tetanus is a symptom and sign complex. The toxin of the tetanus bacillus is one of the most powerful soluble poisons known, the lethal dose for man being 1/300 grain. As regards the incubation period there is some variance of opinion among different authors who have reported series of tetanus cases. Bower (10) regards 8 to 10 days as the usual incubation period;

while Brennan (12) says that 4 to 10 days is the average. Cases are known to have had an incubation period as short as 2 days, and others have been as long as 80 days. Stone in reporting a group of 49 cases (52) finds an average incubation period of 10.8 days. Of the 11 cases at the University hospital (55) the incubation period in most cases was 8 to 10 days. In 4 of the cases the time of injury could not be accurately determined. In massive infections with much necrotic tissue at the focal site the incubation period may be very short. In many instances it is much longer than the average, the bacilli apparently remaining latent in the tissue until subsequently activated by chemical or mechanical irritation. (44)

The premonitory symptoms of tetanus are sore throat, restlessness, irritability and a sense of tightness between the scapulae. In children the first symptom may be a general convulsion which recurs frequently. Often, shooting pains across the back are the first symptoms.

Later, the symptoms progress to stiffness of the neck, the jaw muscles, the esophageal muscles, the abdomen or one or more limbs. There is difficulty in opening the mouth and difficulty in swallowing.

Stiffness increases until a point is reached where sensory stimulation produces a tetanic spasm. Finally spasm becomes constant and usually after four to seven days the jaws become locked (trismus) and they cannot be opened (43).

The corners of the mouth are drawn out due to a spasm of the facial muscles, and the eyebrows are elevated and the forehead is wrinkled. This expression of the face is called the sardonic grin or "risus sardonicus" (56). The voice is often changed. The eyes remain partially closed and the head becomes retracted. Gradually the other muscles of the body become increasingly spastic and opisthotonus or orthotonus may set in on sensory stimulation, producing frightful tonic convulsions accompanied by almost unbearable pain. Occasionally the body is bent to the side (pleurothotonus) and rarely even forward (emprosthotonus) according to Best (10). These convulsions are reflex and may be set in motion by the most trivial stimuli, eg., movement of the bed clothes, a sudden ray of light, etc. Sometimes the back muscles and also the penis is effected.

In a severe case, complete relaxation between convulsions is lacking, the muscles remaining spastic to a lesser degree only and voluntary movements are

impossible of accomplishment. The muscles will remain stiff when anesthesia is induced. Difficulty in swallowing and breathing are common, the latter being accompanied by cyanosis.(41) The convulsions last from a few seconds to several minutes. Fever is not high as a rule, but may reach an agonal height of 113° F. Profuse perspiration is commonly present. Death is usually due to asphyxia or exhaustion; it is practically never of cardiac origin.

With a convulsion the pulse and respiratory rate increase and the temperature usually rises to 102-103° F. The white count runs between 12,000 and 15,000. The spinal fluid is under increased pressure. The mentality is not altered, but the patient suffers great mental anguish due to anxiety. If the treatment is ineffectual, death usually occurs on the 3rd or 4th day of the disease. The patient never dies of the disease, but from its symptoms.(26)

Diagnosis

It cannot be stressed too vigorously that early diagnosis before the classic symptoms have developed is absolutely essential if the mortality from tetanus

is to be effectively lowered. If the simple fact were remembered that stiffness of the jaw, and more especially if accompanied by pain in the back or abdomen, probably heralds a tetanus infection, more lives would be saved (16).

The diagnosis must be based on a history of a wound, on the clinical findings, i.e. symptoms and physical examination. Laboratory studies are probably of value only in a negative way, that is, to rule out other diseases; for example meningitis with a high spinal fluid cell count. Too much store should not be set by the patient's story if he cannot recall a wound or injury, because as I have mentioned before, often it has been too minor an injury for the patient to give any notice to.

Typical tetanus is easily diagnosed from the symptoms described above, but mild or atypical tetanus exists, and may be very difficult to detect. For this reason I will include a classification of the forms of tetanus as proposed by Miller and Rogers (43).

I. Classical Form (Tetanus Descendens)

II. Abnormal Forms

A. Splanchnic----Following Abdominal Surgery

B. Cephalic------Following Head Wounds

1. Non-paralytic
2. Paralytic with facial paralysis
3. Paralytic with oculomotor paralysis
4. Paralytic with hypoglossal paralysis

C. Unilateral

D. Local----Involves only limbs

1. Monoplegic
2. Paraplegic

E. Abdominothoracic

F. Attenuated Form---Long incubation period

G. Tetanus Neonatorum

Miller and Rogers stress the importance of abdominal rigidity. Of 33 cases they reviewed, 24 had abdominal rigidity, and they warn of the pitfall which causes the diagnosis of the condition as an acute abdominal crisis. Many cases of the disease start as localized tetanus, with pain or stiffness first detected around the atrium of infection, or limited to one limb. This may persist for a long time before trismus appears, and tetanus without trismus, its cardinal symptom, has been frequently described (10). Such cases may recover spontaneously, the

incubation period being very prolonged, the toxicity extremely low, and the symptoms limited to a mild, general spasticity of the muscles and a doubtful trismus. About 10% of all cases of generalized tetanus start as a premonitory localized type.

Tetanus neonatorum usually occurs five to eight days after birth, and generally is due to infection of the umbilical stump, but occasionally from circumcision. It is commonest in dairying communities(20).

Although one usually thinks of the "locked jaw", risus sardonicus and a board-like abdomen as characteristic findings in tetanus, some one or all of these particular muscular spasms may be absent.

Differential Diagnosis

Tetanus must be differentiated from:

1. Meningitis
2. Poliomyelitis
3. Tetany
4. Strychnine poisoning
5. Epilepsy
6. Hysteria
7. Rabies

Local conditions of the parotid gland and peritonsillar abscesses may simulate trismus at times, but

lack of the other signs of tetanus make these easily differentiated.

A careful history, when obtainable, a careful physical examination, a check of the deep and superficial reflexes, and an examination of the spinal fluid when indicated, will serve to differentiate all of the above disease states from tetanus relatively easily. In most of them trismus is absent(10).

In tetany the patient is usually a small child. The spasm is accompanied by a characterisitc cry, and it is usually limited to the muscles of the larynx and extremities. Also with tetany the opisthotonus and trismus are not true to type, and the stimulation of certain parts of the body does not produce convulsions.

In strychnine poisoning, symptoms start immediately after assimilation of the drug in toxic doses. Complete relaxation usually occurs between the convulsions and trismus is a rare symptom. According to Dietrich, the ordinary Hinkle pill swallowed by children for their sugar coating, cause a convulsion similar to that of strychnine poisoning (20).

In rabies the history of an animal bite and the fear of water, with the lack of trismus, suffices to

differentiate from tetanus. But tetanus has been reported to follow a dog bite, therefore it cannot be ruled out and rabies ruled in.

Epileptiform convulsions are preceeded by the aura and cry; and both epilepsy and hysteria have many characteristics to differentiate them from tetanus.

In the other diseases of the central nervous system, degenerative, infectious and deficiency; the lack of trismus, the changes in the deep and superficial reflexes, the changes in the spinal fluid and the variable and different response to different stimuli usually suffice to differentiate them from tetanus.

Treatment

The treatment of tetanus is a perplexing problem, to say the least. The reasons for its being such a problem are valid ones. In the first place, and no doubt of the greatest importance is the fact that the pathogenesis of tetanus still has not been completely and exhaustively worked out. We cannot hope to have a specific and absolutely fool-proof treatment for the disease until all the details are known concerning the

alteration of tetanus toxin within the body, and whether the toxin or its primary or perhaps secondary alteration products are responsible for the death of the patient.

Another factor working against the standardization of the best methods of treating tetanus is the relative paucity of cases which any one man, or any one hospital treats, even over long periods of time. The number of cases in each man's series is so small that he cannot be too sure of the value of the methods he uses. In the case of peptic ulcer, rheumatic fever, cholecystitis and the other very common disease entities, treatment becomes standardized along the very best lines, because each physician can reach conclusions from large numbers of his own cases, not to speak of the thousands reported yearly by his colleagues. It is my opinion that the treatment of tetanus could be greatly improved and the mortality figures consequently lowered if the physician would constantly keep before his mind's eye the pathogenesis of the disease.

At this time it is only sensible to realize that with any treatment of tetanus, or any combination of treatments, the recovery rate is far from 100%. In fact it is nearer to 50%. In some instances tetanus

is so acutely fulminating and so overpowering, that one is tempted to say that no matter what stage of perfection therapy reaches, it can never hope to save such cases.

Treatment of tetanus may be divided into three large phases:

1. Immediate propnylaxis
   This is passive immunization, as discussed above under prophylaxis.

2. Long range propnylaxis
   This is active immunization with anatoxin. I am not discussing this because it is a fairly recent, and as yet, an unproved development; and also because this thesis is primarily concerned with treatment rather than propnylaxis.

3. Management of active tetanus.
   This will now be considered.

In discussing active management of tetanus, there are certain main principles which are the whole basis of treatment. As Merkert (42) has so aptly stated "the big problem is to keep the patient alive, and he will get well from his tetanus". Every effort should be directed along four lines:

1. Removal of the nidus of infection

2. Prevention of further absorption of toxin by the central nervous system, and neutralization of circulating toxin.

3. Sedation to control convulsions and reflex spasms.

4. General Care of the Patient: Feeding, Nursing care, Prevention and treatment of complications.

I. Removal of the nidus of infection

Gage and Debakey (26) believe that all tetanus patients should be admitted to the hospital through the operating room, where an immediate debridement should be done. One must constantly keep in mind the anaerobic qualities of the Clostridium tetani and the type of wound in which it will grow. Removal of the nidus of infection doesn't necessarily entail complete excision of the whole wound and the tract of entry of any foreign particle. Kirtley (35) advocates merely incising the infected wound, to convert it into an open wound in which anaerobiasis would be discouraged, if not prevented. On the other hand Meleney (41) thinks complete excision of the wound without closure is a necessity. Taylor (54) makes the statement that "an ounce of clean surgery is worth several pounds of serum therapy", in his support of complete wound excision. Jensen reports (33) that when complete wound

excision is done after the disease develops, the mortality is reduced from 64% to 51%.

Cauterization of the wound which formerly was almost routine in some hospitals now is not done, because it is an utterly illogical treatment, since it brings about the very environment in which the tetanus bacillus thrives. In many instances depending on the judgement of the surgeon, a debridement of crushed and necrotic tissue is all that is necessary to rid the wound of any further toxin producing ability. If the wound is on a toe or finger, involving a nail, the nail should be removed, in the opinion of Cole (17).

Spaeth (51) is against radical immediate wound excision or incision. He prefers to wait until after antitoxin and sedative therapy is well under way. Then after all alarming symptoms and signs have been successfully controlled, a gentle but careful search for foreign bodies is necessary. It is important to remember that a history of removal of foreign bodies prior to hospitalization must not be accepted as final, for residual pieces may remain in the focus of infection.

Cole and Spooner (16) routinely give tetanus antitoxin to the patient before the wound is touched surgically, because any manipulation or interference

with the wound may cause more toxin to pass into the circulation, and if this occurs it is important that there shall be plenty of antitoxin already there to meet it.

After excision or incision of the tetanus infected wound, there are different methods of handling it. Jensen (33) packs the wound lightly with gauze soaked in antitoxin. Others merely syringe the wound out thoroughly with hydrogen peroxide or normal saline; while Meleney (41) floods the wound with a creamy suspension of zinc peroxide. It is important to make certain of the contact of this creamy suspension with every part of the wound. In some cases it is necessary to pack the wound gently with fine-mesh gauze soaked in zince peroxide so as to keep the surfaces of the wound apart; then cover the dressing with vaseline gauze to prevent evaporation.

Local handling of the wound may be summarized thusly: convert an anaerobic environment into one which is aerobic.

II. Prevention of further absorption of toxin by the central nervous system, and neutralization of circulating toxin.

This phase of treatment relates to tetanus

antitoxin therapy. Controversey waxes strongly as to how much and how often antitoxin should be administered; as to the routes to be used for administration; and, surprisingly enough, even as to whether it is essential to use antitoxin or not. I think it important to clear up the latter point first.

A. Is antitoxin necessary ?

Not a few who have discussed the treatment of tetanus in the last five years have expressed some doubt as to whether the administration of tetanus antitoxin to a tetanus case has any value. For example, Huntington et al (32) in 1937 collected 642 cases of tetanus from various nospitals, 72 of which were untreated with antitoxin, and the mortality rate for the 72 was no higher than for those cases treated with antitoxin. No one has ventured to actually state that it has no value, and all give antitoxin in their routine of treatment and also recommend it in the final analysis. The decision whether to use antitetanic serum or not, must be made without delay at the time the patient is first examined.

Abel, in an experiment with dogs (5) has shown that if a certain point is reached in a case of tetanus when a lethal dose of toxin becomes absorbed and fixed,

then antitoxin is no longer of any avail in saving life. "Nevertheless", quoting Abel, "the time has not come when we can say with any degree of certainty that the administration of serum can be dispensed with in human tetanus, unless, indeed, the patient comes to our attention at a time when he is moribund, and intervention of any kind is plainly useless". (5) Who, in the present state of our knowledge, will venture to decide, at the time the patient first comes to hand, whether his tissues have absorbed and fixed a full lethal dose of the toxin, or three-quarters or a half of this amount? It would certainly not be permissible for a physician to make an offhand decision in a case with an ascertained incubation time of 12 or more days, that the use of antitoxin can be dispensed with, on the assumption that his patient has every chance of recovering without it (5).

The use of antitoxin is of great importance in cases of purely local tetanus. In such cases the toxin has reached the muscles neighboring on the nidus of infection by the lymph channels, and as yet has not travelled through the arterial stream to the central nervous system. Therefore by treating the wound in a manner as recommended above, in order to prevent further toxin

elaboration, and administering antitoxin intravenously to combat any small amount of toxin already in the blood stream, a generalized descending tetanus can be prevented.

If we admit, as we must in view of reports, that very little has been accomplished by specific treatment of serious cases of tetanus, it does not necessarily follow that antiserum can be dispensed with. The physician must use it in all cases for he has no way of knowing which case is getting the serum too late to be of any help, and which is getting it in plenty of time to save the life. The time factor is particularly important; a few hours delay in administering antitetanic serum may mean the difference between life and death. Whatever the prognosis of a case of tetanus on admittance, I believe to omit antitoxin therapy is to border on actual negligence.

B. What constitutes adequate serum therapy?

Another point related to antitoxin therapy which is widely and hotly disputed, is how much antitoxin to give and how often it should be given. This variance of opinion is not alarming, because, at least the patient is getting antitoxin, no matter what regime

is followed.

Moore and Singleton (44) state that prior to 1920, no patient received as much as 50,000 units of antitoxin, and their present dosage is an average of 140,000 units per patient. When they began the larger doses of antitoxin the mortality immediately decreased until their last 25 cases have had only a 25% mortality. Kini and Rao (34) recommend 20,000 units of antitoxin twice per day as long as symptoms persist; and they back this up with a mortality of only 50%.

Cables reports a case of tetanus (15) in which the focus of infection was never found, and there was consequently a chronic release of the tetanus toxin into the blood stream. Antitoxin was given over a period of 41 days until all convulsions had ceased; a total of 3,460,000 units were given in all. Boyce and McFetridge (11) believe an average dose of 50,000 units is inadequate, while a dose of over 100,000 units is unnecessary and wasteful.

Spaeth, writing in 1940, believes a single dose of 50,000 units is entirely adequate, and that any more heroic measures along this line is merely wasteful and extravagant, since with this single dose the antitoxin titer in the circulating blood is still very high after 15 days.

Beall, of Texas, treated eight succesive cases with 100% recovery, and gave each only 30,000 units of antitoxin on the first day of observation, and none thereafter (8). Paterson, in Glasgow, in 1938 treated 10 successive cases with an 80% recovery rate and used only an average dose of 27,000 units of antitoxin per patient (46).

The recent trend is definitely toward comparatively small doses of antitoxin, 20,000 to 50,000 units and administered in a single or perhaps two doses.

C. What routes are best for the administration of antitetanic serum?

As for the best route of administration, here again we find controversey. Every possible route has been advocated and used, including: subcutaneous, intramuscular, intravenous and intrathecal (intraspinal and intracisternal). In each instance, statistical support has been offered to justify the route or routes used. This divergence of opinion means that in actual practice no single method has been shown to be much better than another (25).

Merkert (42) declares that the toxin present in an active case of tetanus can be divided into three portions:

1. Toxin fixed to the cells of the brain and cord.

2. Toxin circulating in the bloodstream.

3. Toxin recently elaborated by the focus, and yet in the wound and its immediate vicinity.

Whatever success is to be derived from treatment with tetanus antitoxin comes from neutralization of the latter two portions of the toxin.

Heersema (31) recommends 40,000 units of antitoxin intravenously immediately upon diagnosis, and 40,000 units intravenously four hours later. From theoretical and experimental considerations the intravenous route would appear to have most in its favor, for it is clearly the most rapid way of bringing the antitoxin in contact with nerve cells. The intrathecal route is a less rapid way of sending antitoxin into the general circulation and can only be more efficient if it can affect toxin already in the central nervous system. There is little evidence that this is the case. It also must be recognized that intrathecal injection has several disadvantages, which are:

1. Lumbar puncture must to some degree irritate the nervous system, and to perform it in tetanus, a general anaesthetic is necessary.

2. In order to give sufficient antitoxin, a large amount of cerebrospinal fluid must be withdrawn.

3. The injection of serum into the cerebrospinal fluid is liable to cause a serous meningitis within a few days to some weeks after the injection, and if this occurs when the symptoms of tetanus are still present, it may cause an exacerbation which is serious.

These objections also apply to the cisternal route. (16).

There seems to be little excuse for continuing use of the intrathecal route of administration of serum. There are no good arguments and certainly no clinical evidence to warrant further trial of intrathecal serum. Lazzari and Friedlander mention one of their cases which received intraspinal serum, and at autopsy showed a dense plastic meningitis which is certainly a distinct disadvantage (38). Abel has shown that the injection of antitoxin into the subarachnoid spaces is futile and unnecessary because when large amounts of serum are injected into the subarachnoid space, it is rapidly and completely transferred to the general circulation anyway, and furthermore toxin cannot be demonstrated in any appreciable amounts in the spinal fluid in a case of tetanus (4).

It is Wainwright's opinion that serum given intraspinally is useless and dangerous; useless because toxin is not present in the cerebrospinal fluid, and dangerous because of the aseptic meningitis which can

develop from it (56). Gage and Debakey (26) state "the best way to increase the mortality of tetanus is to give the tetanus antitoxin intrathecally". Brennan (12) reports a case in which 40,000 units of antitoxin were given intraspinally, and he believes this caused more trouble than the tetanus, since the patient developed an aseptic meningitis with severe headache and vomiting.

As is well known, statistics can be made to prove nearly anything, but the following figures of Boyce (11) are enlightening. He reviews 185 cases of tetanus and the mortality for the cases in which the intraspinous route was used was 66%, against a mortality of 56% in cases in which it was not used. Majority opinion seems overwnelmingly opposed to intraspinal administration of tetanus antitoxin, and very much in favor of the intravenous route, supplemented by intramuscular injection around the wound. It seems entirely logical to expect that the only good effects obtained with serum therapy are because it is placed directly into the circulating blood, the only place, outside of the wound itself, where the toxin is capable of being neutralized and rendered inocuous.

Great care must be used in the administration of intravenous serum. It should be given slowly (1 cc.

per minute), diluted in an equal volume of normal saline solution and heated to body temperature (37). The gravity method is most satisfactory. The barrel of a large glass syringe may be used as a container. Attach a #22 needle about 1½ inches long to the syringe barrel with about 15 inches of rubber tubing. There are soluble toxic substances present in new rubber; therefore, all new rubber tubing should be left in a 5% solution of NaOH for 30 minutes before sterilization. (37).

Firor (23) and Merkert (42) among others, especially emphasize the importance of injecting serum intramuscularly, at least 10,000 units by multiple infiltrations, around the site of injury before it is touched surgically, in order to prevent the escape of toxin into the surrounding tissues.

In considering how long serum therapy must be continued, we must use the progress of the patient as the criterion. If convulsions and spasms continue for a long period of time, the intravenous dose of antitetanic serum should be repeated once or twice, until the disease has practically subsided. The desirability of continuing serum treatment depends also on the fate of the antitoxin originally injected. Spooner (16) investigated four cases who had each been given a single

initial dose of 200,000 units, and found that at the end of 14 days there were still between 20,000 and 25,000 units still circulating in the blood. Thus, one would be justified in administering only one adequate dose of antitoxin intravenously, if the disease ran a normal course of 10 to 14 days, and if the causative wound had been properly cared for.

D. Serum Reactions from the use of tetanus antitoxin

Stone (52) writing in 1922 states that serum rashes may be expected about the eighth or tenth day after treatment has started in 50% of those cases receiving antitoxin. While Vener (10) asserts that this complication almost invariably occurs, if not in the form of urticaria, at least as a serum sickness, and it begins at the fourth to fifth day. The urticaria is of an erythematous type. Calcium lactate or Calcium gluconate ¾ grain intravenously will cause a quick subsidence. Calamine lotion applications to the skin give relief, and a subcutaneous injection of 1 cc. of 1:1000 epinephrine is usually of definite benefit. The treatment of these delayed serum sicknesses

may be summarized thusly: topical application of antipruritic agents, oral administration of ephedrine compounds, hypodermic injections of epinephrine hydrochloride 1:1000, Calcium lactate or gluconate intravenously and sedatives may be necessary if the discomfort of the patient becomes too great.

Spaeth (51) mentions the great frequency with which thermal reactions of chills and fever occur, immediately after injection of serum intravenously. These usually last only for a matter of hours and require no particular treatment.

The real fear in giving antitetanic serum is that an acute immediate serum reaction with collapse and possible death will occur. Such a reaction is a true anaphylactic shock. A very careful history is important to detect such cases in advance. History of any serum immunizations or therapeutic serum injections or allergic phenomena of any sort should put the physician on his guard. Sensitivity test are absolutely necessary in every case of tetanus in which serum is going to be administered therapeutically. There tests are also necessary befor a prophylactic injection of 1,500 units is given. The sensitivity test is nearly infallible in detecting cases in which acute accidents

may occur with horse serum. Spaeth (51) prefers the ophthalmic test to the cutaneous test, for although it is less sensitive than the cutaneous test, it is more reliable in predicting acute anaphylactic reactions. In the ophthalmic test one drop of the serum is placed in the conjunctival sac, and a positive reaction is indicated 15 to 20 minutes later if the conjunctiva becomes hyperemic and inflamed. The cutaneous test consists in placing 0.1 cc of toxin intradermally, and if positive an erythematous wheal with pseudopodia will appear. If after the serum injection is commenced, anaphylactic symptoms appear, such as dyspnea, cyanosis or increased pulse rate, stop the injection at once and don't repeat for three hours. After this interval the patient will probably be desensitized by the serum injected in the first attempt and can usually receive the full dose (53).

In the event of an acute serum reaction, epinephrine hydrochloride 1:1000 should be given immediately hypodermically or intravenously if necessary. The foot of the bed should be elevated, external heat with blankets and not water bottles should be applied. If respiratory embarrassment is serious inject 1 cc. coramine hypodermically, use artificial respiration and oxygen.

As a matter of interest which may have some value as it is worked on more extensively, I want to mention the work of Heersema (31) in the past year. He treated a severe case of tetanus, and after the first two days when he seemed to be getting no results with antitetanic serum, he resorted to treatment with an artificial fever cabinet. The patient was given eight fever treatments and recovered from his tetanus.

Now Kligler and his associates (36) state that vitamin C (ascorbic acid) combines with the toxin in tetanus cultures and both are destroyed, and in the human this would result in depletion of the vitamin C content of the blood, and a concomitant detoxification of tetanus toxin in the blood. This detoxification, they found, varies with the temperature and is more efficacious at the nigher temperatures.

Heersema has taken note of this action of vitamin C on the tetanus toxin as reported by Kligler, and he also (Heersema) has found that ascorbic acid blood values are very low in fevers resulting from infection. Thus, he believes that in an infection the ascorbic acid demand is greater than normal and its destruction is greater, owing to the fever or the infectious agent or both. Heersema theorizes that therefore the value of the artificial fever in combating tetanus, is to speed

up the ascorbic acid reaction of detoxification of the tetanus toxin.

III. Sedation to control convulsions and reflex spasms

The action of sedative drugs in controlling convulsions and relaxing spasm of the muscles is becoming recognized as one of the chief, if not the most important measure in treating tetanus. As we have seen above the value of antitoxin therapy is strictly limited because the toxin becomes fixed and altered. This leaves us with only sedation to rely on; and tetanus becomes a problem of controlling convulsions and spasms in order to keep the patient alive. If this can be done effectively, the patient will get over his tetanus infection. Since death from tetanus is a respiratory death brought on by paralysis of the respiratory muscles, and not a death due to toxemia, we see the great importance of using drugs which can exert a strong sedative influence on the body. In severe cases of tetanus, the continued and relentless punishment of the convulsions on the central nervous system has so weakened and drained the individual that the antitoxin has

neither the time or the foundation to exert any influence whatever (50). Adequate sedative action will control all convulsive seizures and allow the patient to have continuous relaxed sleep.

The ideal sedative should produce a quiet, restful narcosis, sustained over a number of hours without associated toxic effects. Every known sedative has been used in tetanus. Morphine, chloral hydrate, paraldehyde and magnesium sulphate were popular ten to twenty years ago. In the past ten years seconal, avertin and sodium amytal have been those used most frequently. According to Bernheim (9) ether, morphine and curare (a motor end-plate poison) are limited in use because of toxicity and depressant effects, while avertin enjoys a wide limit of safety. He recommends 80-125 mg. per kilo of body weight of avertin in divided doses per rectum to control spasms. Avertin gives complete relaxation and freedom from spasms. No evidence of deleterious effects on either the circulatory or respiratory system is seen with avertin. It does not cause increased tolerance or cumulative effects. Avertin does not cause rectal irritation, and after recovery from tetanus the patient is able to sleep without sedatives. Bernheim made repeated urinalyses on avertinized patients and found no signs

of renal irritation. Meleney states (41) that under the influence of avertin the muscles completely lose their hypertonicity. The return of spasm of the muscles even before the patient shows evidence of coming out of the narcosis is an indication for readministration of avertin. Meleney believes avertin to be by far the safest sedative.

Merkert (42) favors avertin as a sedative because it has a protracted effect and is rapidly and completely eliminated. Gage and DeBakey (26) attribute the first use of avertin in tetanus to Laewen of Germany in 1929. They have kept patients completely narcotized with avertin continuously for eight days. Avertin is absorbed rapidly; it is detoxified in the liver and is excreted almost wholly by the kidneys.

Spaeth (51) reports that control of the spasms and the appearance of muscular relaxation follows within five to ten minutes of the administration of avertin if adequate doses are employed. It produces an anesthesia lasting 3 to 5 hours. For children, Spaeth recommends the following dosage:

Initial dose--25 mg. per kilo body weight.

At 30 minute intervals--15 mg. per kilo body weight.

In the presence of rectal irritation, incontinence,

and, or renal or hepatic disorders, avertin should be omitted and another sedative employed.

I have dwelt solely on avertin as the sedative of choice because it seems, and justifiably so, to be enjoying ever-increasing popularity; and I am convinced that it is the safest and best sedative available in tetanus therapy. But I do want to discuss briefly some other sedatives which some physicians advocate and which may have to be resorted to if avertin is contraindicated.

Lyall (39) and Paterson (46) report their use of 2½% magnesium sulphate subcutaneously in doses of 40 cc. each 4 hours. They had good results as far as controlling spasm was concerned, but their chief objection was that the injection of magnesium sulphate caused the patient a good deal of pain. Stone (53) also uses and recommends magnesium sulphate subcutaneously, intravenously and intraspinally, but he admits there is great danger of respiratory distress when it is used. Since tetanus is such an embarrassment to respiration anyway, I would say magnesium sulphate is contraindicated.

The sedatives of the barbiturate series are highly recommended by some authors. Moore and Singleton (44) use luminal, sodium luminal and sodium

amytal in huge doses, as much as 80 grains in 3 days. O'Farrell (45) treats his tetanus cases with nembutal. In one case he used 75 grains intravenously and 63 grains by mouth over a 10 day period, at 7½ grains per dose. He believes the prolonged narcosis was the outstanding beneficial agent in the treament employed, thus bearing out the plea for sedation.

Quoting Dietrich (20), "sedation is clearly indicated before any other therapeutic or diagnostic procedures are undertaken". Dietrich favors seconal for sedation in children. He has used it in 3 cases of tetanus. Seconal controls the convulsions rapidly and well, and yet the preservation of the pharyngeal and cough reflexes has eliminated the fear of aspiration pneumonia. Seconal acts rapidly by mouth or rectum. Dietrich's dose for a 5 year old child is 3 to 4 grains each 3 to 4 hours. There are two main objections to the prolonged use of the drugs of the barbiturate series. First, they are cumulative in action and, secondly they are respiratory depressants and an overdose can cause paralysis of the respiratory center.

West, in 1936 advocated the use of curarine, which is the commonest active principle of curare (57). He gives it by the intravenous drip method. Curarine causes a muscles paralysis by causing a failure of

effective transmission of the impulses travelling to the muscles along the motor nerve. West's mortality with curarine was 90%. Yodh (58) also has used curarine, but he does not recommend it, in fact he condemns it because although it gives a muscular relaxation, a real danger is bronchial spasm and this must be treated by prompt endotracheal intubation.

Bryant and Fairman (13) treated 22 cases of tetanus in Africa with narcosis induced by evipal soluble (evipan sodium). Incidentally, instead of tetanus antitoxin they used injections of sodium sulfapyridine. All of their cases recovered except 5, and they are very enthusiastic in their praise both of evipal soluble and sulfapyridine in the treatment of tetanus.

So we see that any of a number of different sedatives may be used to produce narcosis in tetanus. The primary thing to remember is that narcosis and relaxation must be produced if the life is to be saved. Upon clinical and experimental findings as reported in the literature, I would recommend avertin as the sedtive of choice in all cases unless there were definite contraindications.

IV. General Care of the Patient: Feeding, Nursing care, Prevention and Treatment of Complications

Due to the convulsions and spasms of tetanus there is a constant drain on the nutrition of the body. The emaciation and weakness following a long bout with tetanus are very striking. Consequently it is of the first order of importance to maintain a high caloric daily intake for a case of tetanus. To pass successfully through an ordeal of suffering and prolonged physical exertion such as this, a great deal of food is of vital importance. In an adult an attempt should be made to give at least 2,000 calories daily. Glucose, lemonade and egg and milk are satisfactory foods, and these should be given hourly or more often if the patient is taking food well. Usually tetanus patients are very thirsty and will take fluids well. If feeding is impossible because of severe spasm of the masseters, avertin will give relaxation of the jaws so a stomach tube may be passed (16). The diet should be gradually changed to a soft diet by the end of the second week.

If the patient is unable to swallow, 5% dextrose in saline may be given intravenously during the

first few days. Caution must be exercised not to overload the patient with intravenous fluids. Massive doses are dangerous and may induce pulmonary edema, hypostatic pneumonia and cardiac failure. After the first few days, with assistance, most patients manage to take small amounts of water by mouth (10). Boyce and Mc Fetridge (11) recommend feeding through a nasal-stomach tube. This does away with the danger of hypostatic pneumonia from feeding by vein.

The patient should always be placed in a secluded, quiet, darkened room by himself. Quiet and darkness are especially important since sensory stimulation is the trigger for his convulsions. Visitors are prohibited during the early acute stage. The secret of fine care of a tetanus patient is constant attention day and night by a nurse who understands thoroughly the process going on, and what is being done to stop it. The nearly constant attention of an interne or resident is also needed, and may mean the difference between saving and losing the patient.

In regard to the eliminative functions of the patient, enemas become a necessity if avertin is being used in order that the avertin can be instilled into the rectum. The bladder should be carefully watched

and if retention occurs, catheterization should be resorted to. Despite precautions, patients frequently develop purulent sinusitis. Excessive sedation and poor oral hygiene, associated with mouth breathing and rapid shallow respirations, contribute to a secondary bronchopneumonia. To avoid such complications, postural drainage by moderate elevation of the foot of the bed, and shrinkage of the mucous membrane of the nose, will aid materially (10).

Oral sepsis must be prevented, as far as possible, by gentle suctions, aspiration, or cleansing. Careful attention to this detail will help avoid a fatal secondary aspiration pneumonia. Frequent change of position is essential to avoid pulmonary complications. Resting on the side or abdomen is preferable. If pneumonia does develop to complicate the clinical picture, it usually occurs between the fifth and seventh days, and it requires symptomatic treatment, along with sulfonamides.

In case a sudden severe respiratory spasm occurs, nitrous oxide and oxygen or ether may be necessary until the patient can be put under the influence of a basal anesthetic, Cole (17). If the spasticity of the respiratory muscles becomes too great, death

will occur unless artificial respiration can be accomplished with a Drinker respirator. When cyanosis accompanies the convulsions it is of the greatest importance to determine whether the respiratory difficulty is occasioned by the spasms themselves or by obstruction of the nasopharynx with secretions which cannot be swallowed. If the latter is at fault, removal of the secretions is indicated rather than intensive sedative therapy, Spaeth (51).

Spaeth mentions the frequency of compression fractures of the vertebrae in children because of severe clonic convulsions. If this occurs it must be treated as the same condition would be if uncomplicated by tetanus. Spinal hyperextension is indicated, and with this Spaeth reports that the incidence of residual deformity is very low.

These measures of general care are of extreme importance, not only because they add to the comfort of the patient, but because death from tetanus is so frequently due to a complication such as aspiration pneumonia or cachexia, all of which can be prevented with constant close attention. Since tetanus is admittedly such a potent killer, it certainly merits extraordinary treatment, both medical and nursing. It

cannot be too vigorously stressed that intelligent, agressive nursing care of tetanus patients, is just as important as all the points of medical treatment combined.

Prognosis-Mortality

From the above figures which I have quoted in trying to evaluate the different ways of treating tetanus, it is easily seen that even today the prognosis of any single case is very poor. It is only by looking at a complete series of cases of tetanus that hope can be held out for recovery of a certain number of them. Many factors must be considered in the prognosis of a single case. Most men reporting in the literature consider the period of incubation of the greatest importance. Graffagnino and Davidson (27) conclude after an analysis of their series that the shorter the incubation, the greater is the mortality. Stone (52) reports 49 cases; the overall mortality being 53%, but the mortality of those cases with an incubation of less than 6 days had a mortality of 75%.

Moore and Singleton (44) report 102 cases with a mortality of exactly 50% and their opinion is that a rapid progression of symptoms after the onset, is a more reliable index of a grave prognosis, than is a short incubation period. Their mortality was 57% for those whose symptoms were so severe that they sought hospitalization during the first three days of the disease; while the mortality was only 21% for those who sought hospitalization when the disease had been in progress more than three days.

Brennan (12) shows that the prognosis of tetanus in children is much poorer than in adults, and quoting Osler, he points out, "if the patient survives the tenth day he has an even chance of recovery, and the prognosis improves with each succeeding day. Spaeth, in a recent study of tetanus (51) emphasizes the prognostic importance of both the intensity and frequency of the convulsions. Of 14 cases without convulsions, only one died, whereas, 9 patients out of 16 having convulsions, died.

Complications are another important factor in the prognosis of tetanus. Aspiration pneumonia, which is so great a hazard, offers a grave but not a hopeless prognosis. In a high percentage of cases of tetanus among children, definite compression deformities of the

dorsal vertebrae develop. But rarely does this complication alter the child's chance for recovery.

A study of mortality figures from different hospitals is apt to mislead one, and cause him to have a very pessimistic attitude toward prognosis. But one should realize that these percentages contain all those cases which died within 24 hours after hospital admission, and treatment was sought much too late for it to be of any use at all.

Of the eleven tetanus admissions at the University hospital 1932-1940, 8 died and 3 recovered, a mortality rate of 72.7%, which corresponds to the rate from most hospitals. West (57) reports a personal mortality of 90%, whereas Dietrich (20) reports a series of 13 cases in which 12 recovered and 1 died, a mortality of only 8%. These two reports serve to show very clearly the error in using only a small number of cases to judge prognosis and mortality.

A more definite and more nearly accurate statement can be made regarding mortality after analysis of large numbers of cases. For example, Yodh (58) in observing 438 cases reports a 49.4% cure and a 50.6% mortality. Likewise, Huntington, Thompson and Gordon (32) collected 642 cases from six different hospitals

and the average mortality of the whole group was 63%

I would conclude, therefore, that in any sizeable series of cases of tetanus the minimum mortality expected would be 50%, and the prognosis of any single case would rest on the incubation period, the rapidity of progression of symptoms, the frequency and severity of convulsions and the development of complications.

Conclusion

Because of the manner in which this paper is drawn up, and because I have attempted to draw a definite conclusion at the end of each section in the body of the paper, it would be useless to again summarize the points I have made. But merely for the sake of emphasis I would like to again state the conclusions reached in the sections on Pathogenesis and Treatment.

I. Pathogenesis

The soluble tetanizing toxin produced at the site of the infected wound is carried by the circulating blood from its point of origin to all parts of the body, including the central nervous system and the voluntary muscles.

II. Treatment

All treatment should proceed along one of the four following lines:

1. Removal of the nidus of infection
2. Prevention of further absorption of toxin by the central nervous system, and neutralization of circulating toxin.
3. Sedation to control convulsions and reflex spasms.
4. Intelligent general care of the patient.

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